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54 Pharmaceutical composition and a method for enhancing the absorption of a pharmaceutically active compound.

57 A pharmaceutical composition comprising a pharmaceutically active compound having an absolute bioavailability of not more than 20 % and diltiazem or a pharmaceutically acceptable acid addition salt thereof is disclosed. A method for enhancing the absorption of the pharmaceutically active compound by administering it enterally together with diltiazem or its salt is also disclosed. Diltiazem or its salt is effective to improve or enhance the absorption of said pharmaceutically active compound.

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Pharmaceutical composition and a method for enhancing the  
absorption of a pharmaceutically active compound

This invention relates to a novel pharmaceutical composition and to a method enhancing the absorption of a pharmaceutically active compound. More particularly, it relates to a pharmaceutical composition which comprises a pharmaceutically active compound having an absolute bioavailability of not more than 20 % and diltiazem or a pharmaceutically acceptable acid addition salt thereof.

It is known that diltiazem (chemical name: d-3-acetoxycis-2,3-dihydro-5-(2-(dimethylamino)ethyl)-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one) or a pharmaceutically acceptable acid addition salt thereof is useful as a calcium-antagonistic coronary vasodilator, but the effect of this compound on the absorption of a co-administered drug has not been known.

Pharmaceutically active compounds (or drugs) may be administered by various routes including oral, rectal, sublingual (buccal), intravenous, intramuscular, subcutaneous and topical routes. Among these routes, oral route is generally most convenient. However, oral administration of a drug to patients sometimes gives rise to a great deal of inter-individual difference in the blood concentration of the drug because of variation in absorbability of the drug between each patients, while such blood concentration of the drug may also be affected by a number of other factors such as, for example, solubility

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thereof in gastro-intestinal fluids, stability against chemical or enzymatic decomposition, permeability through gastro-intestinal mucosa or metabolic decomposition in liver. Moreover, bio-availability of a drug is an important factor to elicit the pharmacological effect thereof in living bodies. However, when a drug which shows poor bioavailability is administered orally, it is generally difficult to achieve an adequate blood concentration of the drug. As a matter of course, the blood concentration of such drug may be increased to some extent by increasing the dose thereof, but in this case the drug may cause undesirable side effects.

As a result of various investigations, we have now found that diltiazem or a pharmaceutically acceptable acid addition salt thereof is quite useful to improve or enhance the bioavailability of a pharmaceutically active compound having poor oral bioavailability. Namely, when a pharmaceutically active compound (or drug) has poor bioavailability (i.e., an absolute bioavailability of not more than 20 %), the absorption of said pharmaceutically active compound can be remarkably enhanced by administering it enterally together with diltiazem or a pharmaceutically acceptable acid addition salt thereof. For example, when 40 mg of propranolol hydrochloride (absolute bioavailability: about 4 %) are administered orally to beagle dogs together with 30 mg of diltiazem hydrochloride, said propranolol shows the plasma concentration of about 100 ng/ml, whereas said drug when used

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alone shows the plasma concentration of only about 25 ng/ml.

An object of the present invention is to provide a pharmaceutical composition suitable for use by enteral administration (e.g., oral or rectal administration) and also suitable  
5 for enhancing absorption of a pharmaceutically active compound having an absolute bioavailability of not more than 20 %.

Another object of the invention is to provide a pharmaceutical composition comprising a pharmaceutical active compound having an absolute bioavailability of not more than 20 % and  
10 diltiazem or a pharmaceutically acceptable acid addition salt thereof.

A further object of the invention is to provide a method for enhancing absorption of a pharmaceutically active compound by administering it enterally together with diltiazem or a pharmaceutically acceptable acid addition salt thereof.  
15 These and other objects of the present invention will be apparent to persons skilled in the art from the following description.

In this specification and claims, the terms "absolute bioavailability" is defined as a value which is calculated by  
20 the following formula:

$$\frac{\text{AUC p.o.}}{\text{AUC i.v.}} \times \frac{\text{Dose i.v.}}{\text{Dose p.o.}} \times 100$$

wherein "AUC p.o." and "AUC i.v." stand for the areas under the blood concentration-time curves which are estimated by oral and intravenous administration of a drug. The smaller  
25 the above-mentioned value, the less the amount of a drug which

reaches the systemic circulation. Therefore, the term "absolute bioavailability" always shows the degree of completeness of absorption of a pharmaceutically active compound in systemic circulation.

5           The absorption-enhancing effect of diltiazem is observed in any pharmaceutically active compound having an absolute bioavailability of not more than 20 %. Thus, a wide variety of pharmaceutically active compounds having such absolute bioavailability can be used for the purpose of the present  
10 invention irrespectively of the pharmacological or therapeutic effects thereof, insofar as they do not contraindicate with diltiazem.

Examples of such pharmaceutically active compound include:

15           (i) adrenergic  $\beta$ -blocking agents such as propranolol [chemical name: 1-isopropylamino-3-(1-naphthyloxy)-2-propanol] or alprenolol [chemical name: 1-(2-allylphenoxy)-3-(isopropylamino)-2-propanol];

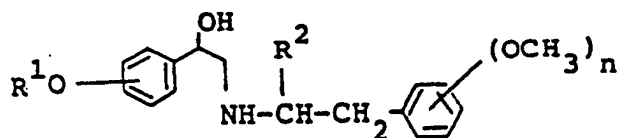
          (ii) catecholamines acting on sympathetic nervous system  
20 such as dopamine, N-L-alanyldopamine [chemical name: N-(L-alanyl)-3,4-dihydroxyphenethylamine], N-L-isoleucyldopamine [chemical name: N-(L-isoleucyl)-3,4-dihydroxyphenethylamine], N-(N-acetylalanyl)-3,4-diethoxycarboxyphenethylamine, N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine or iso-  
25 proterenol;

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(iii) benzodiazepine derivatives acting on central nervous system such as diazepam [chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one] or flurazepam [chemical name: 7-chloro-1-(2-dimethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one];

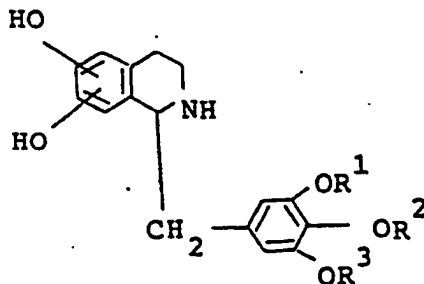
(iv) vasodilators such as isosorbide dinitrate, nitroglycerin or amyl nitrite;

(v) cardiotonics or antidiabetic agents such as benzylalcohol derivatives of the formula:



10 wherein  $R^1$  is hydrogen or alkyl of one to 4 carbon atoms,  $R^2$  is hydrogen or alkyl of one to 4 carbon atoms and  $n$  is an integer of one to 3;

(vi) bronchodilators such as tetrahydroisoquinoline derivatives of the formula:



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wherein each of  $R^1$ ,  $R^2$  and  $R^3$  is hydrogen or alkyl of one to 4 carbon atoms;

(vii) hemostatics such as carbazochrome sulfonic acid [chemical name: 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole-2-sulfonic acid] or adrenochrome monoamino-guanizine;

(viii) antispasmodics such as timepidium halide [chemical name: 1,1-dimethyl-5-methoxy-3-(dithien-2-yl-methylene)-piperidinium halide]; and

10 (ix) antitussives such as tipepidine [chemical name: 3-(di-2-thienylmethylene)-1-methylpiperidine].

The above-mentioned drugs may be used either in free form or in the form of a pharmaceutically acceptable salt thereof. Depending on the physico-chemical characteristics  
15 of the drug, said pharmaceutically acceptable salt may further be either inorganic acid addition salts such as hydrochloride, hydrobromide or sulfate; organic acid addition salts such as citrate, acetate, oxalate, hibenzate (i.e., 2-(4-hydroxybenzoyl)-benzoate) or methanesulfonate; alkali metal salts such as  
20 sodium salt or potassium salt; alkaline earth metal salts such as calcium salt or magnesium salt; amine salts; and the like.

Among the above-mentioned drugs, especially suitable for use in the present invention are propranolol, alprenolol,  
25 dopamine, N-(N-acetylalanyl)-3,4-diethoxycarboxyphenethylamine, N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine,

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diazepam, isosorbide dinitrate,  $\alpha$ -(3,4-dimethoxyphenethyl-aminomethyl)-4-hydroxybenzylalcohol,  $\alpha$ -(3,4-dimethoxyphenethyl-aminomethyl)-3-hydroxybenzylalcohol,  $\alpha$ -[( $\alpha$ -methyl-3,4,5-trimethoxyphenethylamino)methyl]-2-hydroxybenzylalcohol,  
5 trimetoquinol [chemical name: 1-(3,4,5-trimethoxybenzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), 1-(3,4,5-trimethoxybenzyl)-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole-2-sulfonic acid, timepidium halide, tipepidine and a pharmaceutically acceptable  
10 salt thereof.

On the other hand, diltiazem to be used together with the pharmaceutically active compound may be used in the form of either free base or a pharmaceutically acceptable acid addition salt thereof. Examples of the pharmaceutically  
15 acceptable acid addition salt of diltiazem include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, nitrate or perchlorate; and organic acid addition salts such as acetate, oxalate, malonate, tartrate, citrate, lactate or aspartate.

20 The dose of the pharmaceutically active compound to be used together with diltiazem or an acid addition salt thereof is not critical, but is preferably used within its usual dosage range. For example, propranolol or its salt is preferably used at a dose of 15 to 90 mg/day/body; alprenolol  
25 or its salt at a dose of 50 to 200 mg/day/body; dopamine or its salt at a dose of 200 to 1,000 mg/day/body; N-(N-acetyl-



alanyl)-3,4-diethoxycarboxyphenethylamine at a dose of 500 to 3,000 mg/day/body; N-(N-acetylmethyl)-3,4-diethoxycarboxyphenethylamine at a dose of 500 to 3,000 mg/day/body; diazepam or its salt at a dose of 4 to 20 mg/day/body; isosorbide  
5 dinitrate at a dose of 15 to 40 mg/day/body;  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzylalcohol or its salt at a dose of 5 to 50 mg/day/body;  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-3-hydroxybenzylalcohol or its salt at a dose of 4 to 60 mg/day/body;  $\alpha$ -[( $\alpha$ -methyl-3,4,5-trimethoxyphenethylamino)-  
10 methyl]-2-hydroxybenzylalcohol or its salt at a dose of 5 to 60 mg/day/body; trimethoquinol or its salt at a dose of 4 to 12 mg/day/body; 1-(3,4,5-trimethoxybenzyl)-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or its salt at a dose of 2 to 12 mg/day/body; carbazochrome sulfonic acid or its salt at a  
15 dose of 30 to 90 mg/day/body; timepidium halide at a dose of 50 to 100 mg/day/body; and tipepidine or its salt at a dose of 60 to 150 mg/day/body, respectively.

On the other hand, diltiazem or a pharmaceutically acceptable acid addition salt thereof to be used for enhancing  
20 the absorption of the pharmaceutically active compound is preferably used at a dose of 5 to 500 mg/day/body, especially 20 to 360 mg/day/body.

The pharmaceutically active compound having an absolute oral bioavailability of not more than 20 % and diltiazem or a  
25 pharmaceutically acceptable acid addition salt thereof should preferably be used within the weight ratio of from 1 : 200 to

- 100 : 1, especially from 1 : 100 to 50 : 1, more especially from 2 : 100 to 20 : 1. For example, the preferred weight ratio of said pharmaceutically active compound to diltiazem or a salt thereof can be shown illustratively as follows:
- 5 from 0.2 : 1 to 3 : 1, especially from 0.25 : 1 to 0.75 : 1 for propranolol or its salt; from 0.1 : 1 to 3.0 : 1, especially from 0.2 : 1 to 2 : 1 for alprenolol or its salt; from 2 : 1 to 40 : 1, especially from 2 : 1 to 10 : 1 for dopamine or its salt; from 1 : 1 to 100 : 1, especially from 1 : 1 to 25 : 1
- 10 for N-(N-acetylalany)-3,4-diethoxycarboxyphenethylamine; from 1 : 1 to 100 : 1, especially from 1 : 1 to 25 : 1 for N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine; from 0.04 : 1 to 0.8 : 1, especially from 0.06 : 1 to 0.2 : 1 for diazepam or its salt; from 0.08 : 1 to 3 : 1, especially from
- 15 0.1 : 1 to 0.8 : 1 for isosorbide dinitrate; from 0.1 : 1 to 1 : 1, especially from 0.14 : 1 to 0.5 : 1 for  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzylalcohol or its salt; from 0.12 : 1 to 0.8 : 1, especially from 0.17 : 1 to 0.5 : 1 for  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-3-hydroxy-
- 20 benzylalcohol or its salt; from 0.12 : 1 to 1 : 1, especially from 0.17 : 1 to 0.5 : 1 for  $\alpha$ -[( $\alpha$ -methyl-3,4,5-trimethoxyphenethylamino)methyl]-2-hydroxybenzylalcohol or its salt; from 0.02 : 1 to 0.8 : 1, especially from 0.03 : 1 to 0.2 : 1 for trimethoquinol or its salt; from 0.024 : 1 to 0.4 : 1, especially from 0.03 : 1 to 0.1 : 1 for 1-(3,4,5-trimethoxy-
- 25 benzyl)-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or its

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salt; from 0.2 : 1 to 6 : 1, especially from 0.25 : 1 to 1.5 : 1 for carbazochrome alkali metal sulfonate; from 0.18 : 1 to 18 : 1, especially from 0.25 : 1 to 4.5 : 1 for timepidium halide; and from 0.3 : 1 to 14 : 1, especially from 0.4 : 1 to 4 : 1 for tipepidine or its salt.

The pharmaceutically active compound having an absolute oral bioavailability of not more than 20 % and diltiazem or a pharmaceutically acceptable acid addition salt thereof may be administered to a warm-blooded animal including man through conventional enteral route, for example, by oral route or rectal route. Further, these components may be administered in the form of a conventional preparation, for example, in a solid dosage form such as tablets, pills, powders, granules or suppositories; or in a liquid dosage form such as solutions, syrups, emulsions, elixirs, suspensions or lemonades. In formulating these preparations, there may be used a pharmaceutically acceptable carrier or diluent such as binders (e.g., syrup, arabic gum, gelatin, sorbit, tragacanth, polyvinylpyrrolidone), diluents (lactose, sucrose, corn starch, calcium phosphate, sorbit), lubricants (e.g., magnesium stearate, talc, polyethylene glycol, silica), disintegrators (e.g., corn starch), wetting agents (e.g., sodium lauryl sulfate) and suppository bases (e.g., cacao butter, laurin butter, polyethylene glycol (e.g., macrogol), glycerinated gelatin, triglyceride of saturated fatty acids ( $C_{12} - C_{18}$ ) (e.g., Witepsol)). Flavoring agents, sweetening agents or

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coloring agents may also be added thereto.

The pharmaceutical composition of the present invention may be in the form of a single preparation containing both the pharmaceutically active compound and diltiazem or its salt. Alternatively, each components of the invention, i.e., the pharmaceutically active compound and diltiazem or its salt, may be formulated into separate preparations to be used simultaneously for patients, e.g., into a unit-dosage-pack containing each components separately.

10 Diltiazem or a pharmaceutically acceptable acid addition salt thereof can enhance the absorption of a pharmaceutically active compound insofar as said pharmaceutically active compound is the one having an absolute bioavailability of not more than 20 %, and hence, can increase the concentration of  
15 said pharmaceutically active compound in blood. Therefore, diltiazem or its salt when administered enterally together with the pharmaceutically active compound can improve the bioavailability of said pharmaceutically active compound and can also reduce doses of said co-administered active compound.  
20 The simultaneous administration of the pharmaceutically active compound and diltiazem or its salt is further advantageous to reduce inter-individual variation in the pharmacological effect of the pharmaceutically active compound, whereas oral administration of the pharmaceutically active compound sometimes  
25 brings about large variation in the pharmacological effects thereof between each patients due to difference in the bioa-

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vailability thereof. Additionally, the simultaneous administration of propranolol (adrenergic  $\beta$ -blocking agent) and diltiazem may be advantageous for treatment of coronary heart diseases (e.g., angina pectoris) in that both of the decrease  
5 in cardiac output caused by propranolol and the coronary vasodilating action of diltiazem serves to improve the disease state of patients. Further, the simultaneous administration of  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzylalcohol (cardiotonic agent) and diltiazem is advantageous for treatment  
10 of patients without undesirable effects on heart rate because a possible increase in heart rate caused by the former compound is compensated by diltiazem.

The present invention is illustrated by the following Experiments and Examples but should not be construed to be  
15 limited thereto.

#### Experiment 1

The experiment was performed in 10 patients with ischemic heart disease. 20 mg of propranolol hydroxhloride  
20 and 30 mg of diltiazem hydrochloride were administered orally to the patients 3 times daily for 4 days. As a result, the mean steady state plasma concentration of propranolol measured on the last day of the experiment was 34.7 ng/ml. On the other hand, when 20 mg of propranolol hydrochloride were  
25 administered orally to the same patients 3 times daily for 4 days, the mean steady state plasma concentration of propranolol

measured on the last day of the experiment was 24.7 ng/ml.

It is clear from the above-mentioned results that the plasma concentration of proterenolol was increased by the simultaneous administration of diltiazem hydrochloride.

5     Experiment 2

          The experiment was performed in 4 male beagle dogs (mean body weight: 12 kg) fasted for 24 hours. 40 mg of propranolol hydrochloride were administered orally to the beagle dogs. After one week interval, 40 mg of propranolol hydrochloride and 30 mg of diltiazem hydrochloride were administered orally to the same beagle dogs. After another one week, 40 mg of propranolol hydrochloride and 60 mg of diltiazem hydrochloride were administered orally to the same beagle dogs. The plasma propranolol concentration was examined at intervals. The results are shown in the following Table 1.

          It is clear from Table 1 that diltiazem hydrochloride enhanced the absorption of propranolol hydrochloride.

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Table 1

Dosing conditions	Plasma propranolol concentration (ng/ml)						
	Time after oral administration (hr)						
	0.5	1	2	3	4	5	6
PL* 40 mg	18.6	28.7	29.2	21.1	14.6	9.4	5.2
PL 40 mg + DT** 30 mg	35.2	71.7	100.4	72.3	48.4	41.7	21.5
PL 40 mg + DT 60 mg	22.2	106.2	169.6	161.5	102.9	67.9	48.4

Note: \* : PL stands for propranolol hydrochloride  
 \*\* : DT stands for diltiazem hydrochloride

### 10 Experiment 3

Male beagle dogs (body weight: 12 to 14 kg; one group: 3 to 8 beagle dogs) fasted for 24 hours were used in each groups. A drug having an absolute bioavailability of not more than 20 % and diltiazem hydrochloride were administered orally to the beagle dogs. After one week intervals, the drug only was administered orally to the same beagle dogs. The plasma drug concentration was examined at intervals by gas chromatography if the drug was diazepam; by TCL densitometry if the drug was propranolol hydrochloride or timepidium bromide; or by high-peformance liquid chromatography if the drug was tipepidine hibenzate or carbazochrome sodium sulfate.

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Based on the results obtained above, the absorption enhancing effect of diltiazem hydrochloride was calculated by the following formula;

Absorption enhancing effect

$$= \frac{\text{Area under the plasma drug concentration-time curve estimated by co-administration of the drug and diltiazem hydrochloride}}{\text{Area under the plasma drug concentration-time curve estimated by administration of the drug only}}$$

The results are shown in the following Table 2.

Table 2

Drug and its dose	Dose of diltiazem hydrochloride	Absorption enhancing effect
Propranolol hydrochloride (20 mg).	30 mg	3.9
Diazepam (4 mg)	30 mg	2.85
Timepidium bromide (300 mg)	30 mg	2.3
Tipepidine hibenzate (50 mg)	60 mg	2.1
Carbazochrome sodium sulfonate (100 mg)	60 mg	1.9



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Example 1

(Capsules)

	propranolol hydrochloride	15.0 g
	diltiazem hydrochloride	60.0 g
5	starch	20.0 g
	lactose	194.0 g
	polyvinylpyrrolidone	10.0 g
	magnesium stearate	0.7 g
	hydrated silicic acid	0.3 g
10	Total	300 g

A mixture of propranolol hydrochloride, diltiazem hydrochloride, starch and lactose is added to an ethanol solution of polyvinylpyrrolidone. The mixture is kneaded, granulated and then dried. Magnesium stearate and hydrated silicic acid are added to the dried granules, and the mixture is filled into capsules in an amount of 300 mg per capsule.

Example 2

(Tablets)

	propranolol hydrochloride	20.0 g
20	diltiazem hydrochloride	30.0 g
	starch	10.0 g
	lactose	122.8 g
	polyvinylpyrrolidone	6.0 g
	magnesium stearate	1.2 g
25	Total	190 g

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A mixture of propranolol hydrochloride, diltiazem hydrochloride, starch and lactose is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate is added to the dried granules, and the mixture is compressed into tablets of 8 mm in diameter (average weight per each tablets: 190 mg).

Example 3

(Capsules)

	alprenolol hydrochloride	15.0 g
10	diltiazem hydrochloride	60.0 g
	starch	20.0 g
	- lactose	194.0 g
	polyvinylpyrrolidone	10.0 g
	magnesium stearate	0.7 g
15	<u>hydrated silicic acid</u>	<u>0.3 g</u>
	Total	300 g

A mixture of alprenolol hydrochloride, diltiazem hydrochloride, starch and lactose is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate and hydrated silicic acid are added to the dried granules, and the mixture is filled into capsules in an amount of 300 mg per capsule.

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Example 4

(Tablets)

	trimetoquinol hydrochloride	3.0 g
	diltiazem hydrochloride	50.0 g
5	lactose	115.0 g
	polyvinylpyrrolidone	6.0 g
	carboxymethylcellulose calcium	24.5 g
	<u>magnesium stearate</u>	<u>1.5 g</u>
	Total	200 g

10 A mixture of trimetoquinol hydrochloride, diltiazem hydrochloride and lactose is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate and carboxymethylcellulose calcium are added to the dried granules, and the mixture is

15 compressed into tablets of 8 mm in diameter (average weight per each tablets: 200 mg).

Example 5

(Granules for making syrups)

	tipepidine hibenazate	2.0 g
20	diltiazem citrate	2.3 g
	anhydrous glucose	70.0 g
	lactose	23.0 g
	hydroxypropylcellulose	1.0 g
	monosodium fumarate	1.0 g
25	hydrated silicic acid	0.3 g
	flavors	a sufficient quantity
	Total	100 g

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A mixture of tipepidine hibenzate, diltiazem citrate, anhydrous glucose, lactose and monosodium fumarate is added to an ethanol solution of hydroxypropylcellulose, and the mixture is kneaded, granulated and then dried. Hydrated  
 5 silicic acid and flavors are added to the dried granules. The thus-obtained granules are used to make syrups.

Example 6

(Suppositories)

	N-(N-acetylmethionyl)-3,4-	
10	dimethoxycarboxyphenethylamine	200.0 g
	diltiazem hydrochloride	60.0 g
	triglyceride of fatty acid (C <sub>12</sub> - C <sub>18</sub> )	
	(i.e., Witepsol W-35)	1340 g
<hr/>		
15	Total	1600 g

Witepsol W-35 is melted at 60°C and then cooled to 40 °C. N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine and diltiazem hydrochloride are added to the Witepsol W-35, and the mixture is blended homogeneously for about 20 minutes.  
 20 The resultant mixture is poured into a suppository mold and then allowed to stand at room temperature to give suppositories (average weight of each suppositories: 1.6 g) each containing 200 mg of N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine and 60 mg of diltiazem hydrochloride.

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Example 7

(Tablets)

	$\ell$ -1-(3,4,5-trimethoxybenzyl)-5,7-	
	dihydroxy-1,2,3,4-tetrahydro-	3.0 g
5	isoquinoline hydrochloride	
	diltiazem hydrochloride	50.0 g
	lactose	115.0 g
	polyvinylpyrrolidone	6.0 g
	carboxymethylcellulose calcium	24.5 g
10	<u>magnesium stearate</u>	<u>1.5 g</u>
	Total	200 g

A mixture of  $\ell$ -1-(3,4,5-trimethoxybenzyl)-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, diltiazem hydrochloride and lactose is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate and carboxymethylcellulose calcium are added to the dried granules, and the mixture is compressed into tablets of 8 m in diameter (average per each tablets: 200 mg).

20 Example 8

(Capsules)

	N-(N-acetylmethionyl)-3,4-diethoxy-	
	carboxyphenethylamine	200.0 g
	diltiazem hydrochloride	160.0 g
25	starch	130.0 g
	polyvinylpyrrolidone	15.0 g
	<u>magnesium stearate</u>	<u>5.0 g</u>
	Total	510 g

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A mixture of N-(N-acetylmethionyl)-3,4-diethoxycarboxy-phenethylamine, diltiazem hydrochloride and starch is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate is added to the dried granules, and the mixture is filled into capsules in an amount of 510 mg per capsule.

Example 9

(Capsules)

	N-(N-acetylalanyl)-3,4-diethoxy-	
10	carboxyphenethylamine	200.0 g
	diltiazem hydrochloride	160.0 g
	starch	130.0 g
	polyvinylpyrrolidone	15.0 g
	<u>magnesium stearate</u>	<u>5.0 g</u>
15	Total	510 g

A mixture of N-(N-acetylalanyl)-3,4-diethoxycarboxy-phenethylamine, diltiazem hydrochloride and starch is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate is added to the dried granules, and the mixture is filled into capsules in an amount of 510 mg per capsule.

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Example 10

(Capsules)

	dopamine hydrochloride	300.0 g
	diltiazem hydrochloride	100.0 g
5	starch	79.0 g
	polyvinylpyrrolidone	16.0 g
	magnesium stearate	5.0 g
<hr/>		
	Total	500 g

A mixture of dopamine hydrochloride, diltiazem hydrochloride and starch is added to an ethanol solution of polyvinylpyrrolidone, and the mixture is kneaded, granulated and then dried. Magnesium stearate is added to the dried granules, and the mixture is filled into capsules in an amount of 500 mg per capsule.

15 Example 11

(Tablets)

	$\alpha$ -(3,4-dimethoxyphenethylamino-	
	methyl)-4-hydroxybenzylalcohol	100.0 g
	diltiazem hydrochloride	250.0 g
20	starch	50.0 g
	crystalline cellulose	792.0 g
	magnesium stearate	8.0 g
<hr/>		
	Total	1200 g

The above-mentioned ingredients are mixed, and the mixture is compressed into tablets of 7 mm in diameter (average weight per each tablets: 120 mg).

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Example 12

(Tablets)

	$\alpha$ -(3,4-dimethoxyphenethylamino-	
	methyl)-3-hydroxybenzylalcohol	100.0 g
5	diltiazem hydrochloride	250.0 g
	starch	50.0 g
	crystalline cellulose	792.0 g
	<u>magnesium stearate</u>	<u>8.0 g</u>
	Total	1200 g

10 The above-mentioned ingredients are mixed, and the mixture is compressed into tablets of 7 mm in diameter (average weight per each tablets: 120 mg).

Example 13

(Tablets)

15	$\alpha$ -( $\alpha$ -methyl-3,4,5-trimethoxy-	
	phenethylamino)methyl)-2-	
	hydroxybenzylalcohol	100.0 g
	diltiazem hydrochloride	250.0 g
	starch	50.0 g
20	crystalline cellulose	792.0 g
	<u>magnesium stearate</u>	<u>8.0 g</u>
	Total	1200 g

25 The above-mentioned ingredients are mixed, and the mixture is compressed into tablets of 7 mm in diameter (average weight per each tablets: 120 mg).



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Example 14

(Capsules)

	carbazochrome sodium sulfonate	30.0 g
	diltiazem hydrochloride	60.0 g
5	crystalline cellulose	207.0 g
	<u>magnesium stearate</u>	<u>3.0 g</u>
	Total	300 g

The above-mentioned ingredients are mixed, and the mixture is filled into capsules in an amount of 300 mg per capsule.

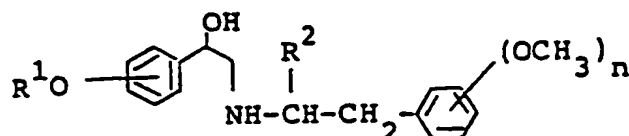
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CLAIMS:

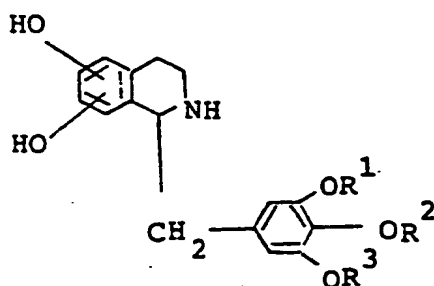
1. A pharmaceutical composition which comprises an effective amount of a pharmaceutically active compound having an absolute bioavailability of not more than 20 %, and diltiazem or a pharmaceutically acceptable acid addition salt thereof.
2. The pharmaceutical composition according to Claim 1, wherein the weight ratio of the pharmaceutically active compound to diltiazem or a pharmaceutically acceptable acid addition salt thereof is from 1 : 200 to 100 : 1.
3. The pharmaceutical composition according to Claim 1, wherein the weight ratio of the pharmaceutically active compound to diltiazem or a pharmaceutically acceptable acid addition salt thereof is from 1 : 100 to 50 : 1.
4. The pharmaceutical composition according to Claim 1, wherein the weight ratio of the pharmaceutically active compound to diltiazem or a pharmaceutically acceptable acid addition salt thereof is from 2 : 100 to 20 : 1.
5. The pharmaceutical composition according to Claim 1, wherein the pharmaceutically active compound is a member selected from the group consisting of propranolol, alprenolol, dopamine, N-L-alanyldopamine, N-L-isoleucyldopamine,

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N-(N-acetylalanyl)-3,4-diethoxycarboxyphenethylamine,  
 N-(N-acetylmethionyl)-3,4-diethoxycarboxyphenethylamine,  
 isoproterenol, diazepam, flurazepam, isosorbide dinitrate,  
 nitroglycerin, amyl nitrite, a benzylalcohol derivative of  
 5 the formula:



10 wherein  $R^1$  is hydrogen or alkyl of one to 4 carbon atoms,  $R^2$  is hydrogen or alkyl of one to 4 carbon atoms and  $n$  is an integer of one to 3, a tetrahydroisoquinoline derivative of the formula:



15 wherein each of  $R^1$ ,  $R^2$  and  $R^3$  is hydrogen or alkyl of one to 4 carbon atoms, 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole-2-sulfonic acid, adrenochrome monoaminoguanizine, timepidium halide, tipepidine and a pharmaceutically acceptable salt thereof.

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6. The pharmaceutical composition according to Claim 1, wherein the pharmaceutically active compound is a member selected from the group consisting of propranolol, alprenolol, dopamine, N-(N-acetylalanyl)-3,4-diethoxycarboxy-phenethylamine, N-(N-acetylmethionyl)-3,4-diethoxycarboxy-phenethylamine, diazepam, isosorbide dinitrate,  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzylalcohol,  $\alpha$ -(3,4-dimethoxyphenethylaminomethyl)-3-hydroxybenzylalcohol,  $\alpha$ -[( $\alpha$ -methyl-3,4,5-trimethoxyphenethylamino)methyl]-2-hydroxybenzyl-  
alcohol, trimetoquinol, 1-(3,4,5-trimethoxybenzyl)-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole-2-sulfonic acid, timepidium halide, tipepidine and a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition according to Claim 1, which is in the dosage form suitable for oral administration.

8. The pharmaceutical composition according to Claim 1, which is in the dosage form suitable for rectal administration.

9. A method for enhancing the absorption of a pharmaceutically active compound (said pharmaceutically active compound having an absolute bioavailability of not

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more than 20 %) in a warm-blooded animal, which comprises administering enterally an effective amount of said pharmaceutically active compound together with diltiazem or a pharmaceutically acceptable acid addition salt thereof to  
5 said warm-blooded animal.

10. The method according to Claim 9, wherein the pharmaceutically active compound and diltiazem or a pharmaceutically acceptable acid addition salt thereof are  
10 administered at the weight ratio of from 1 : 200 to 100 : 1.

11. The method according to Claim 9, wherein the pharmaceutically active compound and diltiazem or a pharmaceutically acceptable acid addition salt thereof are  
15 administered at the weight ratio of from 1 : 100 to 50 : 1.

12. The method according to Claim 9, wherein the pharmaceutically active compound and diltiazem or a pharmaceutically acceptable acid addition salt thereof are  
20 administered at the weight ratio of from 2 : 100 to 20 : 1.

13. The method according to Claim 9, wherein the pharmaceutically active compound claimed in Claim 5 and diltiazem or a pharmaceutically acceptable acid addition salt  
25 thereof are administered to said warm-blooded animal.

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14. The method according to Claim 9, wherein the pharmaceutically active compound claimed in Claim 6 and diltiazem or a pharmaceutically acceptable acid addition salt thereof are administered to said warm-blooded animal.

5 15. The method according to Claim 9, wherein the pharmaceutically active compound and diltiazem or a pharmaceutically acceptable acid addition salt thereof are administered by oral route.

10 16. The method according to Claim 9, wherein the pharmaceutically active compound and diltiazem or a pharmaceutically acceptable acid addition salt thereof are administered by rectal route.